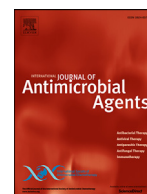




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Letter to the Editor

Effect of hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial, an update with an intention-to-treat analysis and clinical outcomes[☆]



We agree with colleagues that excluding six patients from our analysis may have biased its results [1]. For that reason, we re-analyzed our data about all 42 patients initially enrolled in our survey, including those transferred to intensive care unit (ICU). In this updated analysis, in addition to viral clearance over time, we analyzed chronic conditions of patients and clinical outcomes, including results of NEWS severity score [2], need for oxygen therapy, transfer to ICU, death and length of hospital stay. In our study, missing data of PCR results were considered positive if the results of PCR performed the day before and the day after were positive. Contrariwise, they were considered negative if the results of at least one of the previous 2 consecutive days were negative.

Mean age was significantly higher in patients who received hydroxychloroquine (HCQ) treatment only or in combination with azithromycin (AZ); chronic conditions were significantly more common in both treated groups and, as expected, lower-tract respiratory infections (LRTI) were more common in patients treated with HCQ-AZ. NEWS scores on admission, requirement for oxygen therapy, transfer to ICU and death did not significantly differ between groups. Length of stay at hospital and viral persistence were significantly shorter in treated patients, compared to controls. Length of stay was calculated for 38 of the 42 patients because two patients died, one was discharged against medical advice and information was missing for one patient (Table 1).

In addition, using logistic and linear regression models, we calculated adjusted Odds ratio (OR) of contagiousness at day 7. Patients with two consecutive negative PCR results at least 24 hours apart were considered non-contagious [3]. We also calculated the

Table 1
Characteristics of the populations studied

	Total (N = 42)		Control patients (standard care) (N = 18)		Hydroxychloroquine treatment only (N = 16)		Hydroxychloroquine and azithromycin combined treatment (N = 8)		p-value ^a
	n	%	n	%	n	%	n	%	
Gender									
Male	19	45.2	7	38.9	7	36.8	5	26.3	0.66
Female	23	54.8	11	61.1	9	39.1	3	13.0	
Age									
Mean ± SD	47.7 ± 23.0		37.8 ± 23.0		55.8 ± 21.2		53.9 ± 18.8		0.09**
Min - max	10 - 89		10 - 75		24 - 87		20 - 89		
Chronic diseases (n = 41)									
Hypertension	8	19.5	1	5.9	6	37.5	1	12.5	0.06
Diabetes	2	4.9	1	5.9	1	6.2	0	0	1.0
Coronapathology	1	2.4	0	0	1	6.2	0	0	0.58
Obesity	1	2.4	0	0	1	6.2	0	0	0.58
At least one chronic disease	9	22.0	1	5.9	7	43.8	1	12.5	0.03
Time between the onset of symptoms and hospitalization (n = 34)									
Mean ± SD	5.4 ± 5.0		3.7 ± 2.7		4.6 ± 4.0		9.5 ± 7.2		0.13**
Min - max	0 - 23		0 - 10		0 - 11		1 - 23		
Respiratory symptoms at inclusion									
Asymptomatic	6	14.3	4	22.2	2	12.5	0	0.0	0.46
Upper respiratory tract infections	22	52.4	10	55.6	10	62.5	2	25.0	0.21
Lower respiratory tract infections	14	33.3	4	22.2	4	25.0	6	75.0	0.03
NEWS score									
0 - 4 (low)	35	83.3	16	88.9	13	81.2	6	75.0	0.65
5-6 (medium)	2	4.8	0	0	1	6.2	1	12.5	0.32
≥ 7 (high)	5	11.9	2	11.1	2	12.5	1	12.5	1.0
Mean ± SD	2.0 ± 3.2		1.4 ± 3.3		2.1 ± 2.6		2.9 ± 4.1		0.26**
Min - max	0 - 13		0 - 13		0 - 8		0 - 12		

(continued on next page)

[☆] This article refers to 10.1016/j.ijantimicag.2020.106171 and 10.1016/j.ijantimicag.2020.105949.

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Table 1
(continued)

	Total (N = 42)		Control patients (standard care) (N = 18)		Hydroxychloroquine treatment only (N = 16)		Hydroxychloroquine and azithromycin combined treatment (N = 8)		p-value*
	n	%	n	%	n	%	n	%	
Clinical outcomes									
Oxygen therapy	8	19.0	2	11.1	2	12.5	4	50.0	0.07
Transfer to intensive care unit	5	11.9	1	5.6	2	12.5	2	25.0	0.31
Death	2	4.8	0	0	1	6.2	1	12.5	0.32
Length of stay in hospital (N = 38)									
Mean \pm SD	9.8 \pm 7.3		12.1 \pm 9.6		8.6 \pm 5.2		7.1 \pm 3.2		0.04**
Min - max	2 - 47		6 - 47		2 - 24		4 - 14		
Negativity of virus by RT-PCR									
Day3 (n = 41)	12	29.3	2	11.1	5	31.2	5	71.4	0.01
Day4 (n = 40)	17	42.5	5	27.8	7	43.8	5	83.3	0.07
Day5 (n = 40)	17	42.5	4	22.2	7	43.8	6	100	0.003
Day6 (n = 40)	17	42.5	3	16.7	8	50.0	6	100	0.001
Day7 (n = 36)	17	47.2	4	28.6	7	46.7	6	85.7	0.051
Lack of contagion at Day 7	15	35.7	3	16.7	7	43.8	5	62.5	0.07

* one-sided Fisher's exact test.

** Kruskal-Wallis test.

adjusted coefficient for length of hospital stay. Results with a p value <0.05 and 95% confidence interval excluding 1 were considered statistically significant. Statistical analysis was conducted using R (R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, 2020. URL: <https://www.Rproject.org/>). The increase in length of hospital stay was found to be associated with male sex (adjusted Coefficient=5.76, CI [1.33 - 10.18], p=0.01) and LRTI symptoms on admission (adjusted Coefficient=6.84, CI [1.01 - 12.66], p=0.02). Treatment with HCQ-AZ is associated with decreased contagiousness at Day 7 (adjusted OR =0.08, CI [0.01 - 0.40], p=0.016) and reduced length of hospital stay (adjusted coefficient =-12.54, CI [-18.96 - -6.11], p<0.0001) (supplementary Table 1).

In conclusion, the reintegration of excluded patients in our analysis and the adjunction of clinical outcomes confirm the effectiveness of the combination HCQ-AZ on both viral clearance and early discharge of COVID-19 patients when treated early in the course of the disease. Since this preliminary work was done, we have been able to follow at our institute, 3,737 COVID-19 patients, including 3,119 (83.5%) treated with HCQ-AZ for at least three days and 618 (16.5%) patients treated with other regimens. Treatment with HCQ-AZ was associated with a decreased risk of transfer to ICU or death (Hazard ratio (HR) 0.18 0.11–0.27), a decreased risk of hospitalization ≥ 10 days (odds ratios 95% CI 0.38 0.27–0.54) and a shorter duration of viral shedding (time to negative PCR: HR 1.29 1.17–1.42) [4]. These results conducted in a large cohort of patients at a single center and analyzed using more robust statistical tests, clearly confirm our preliminary results obtained and published in a hurry with some weaknesses and imperfections [5].

Declaration of Competing Interest

The authors declare no competing interests.

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Ethical approval

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.ijantimicag.2020.106239](https://doi.org/10.1016/j.ijantimicag.2020.106239).

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